

ORIGINAL ARTICLE

Chronic myeloid leukemia outcomes according to baseline risk and first-line treatment in real-world settings: Data from the Italian Network/CML Campus

Valentina Gai MD, PhD¹  | Tiziana Rosso MSc, PhD² |
 Fausto Castagnetti MD, PhD³ | Patrizia Pregno MD¹ |
 Massimiliano Bonifacio MD, PhD⁴  | Isabella Capodanno MD⁵ |
 Mario Tiribelli MD, PhD⁶  | Fabio Stagno MD, PhD⁷ | Giovanni Caocci MD, PhD⁸ |
 Antonella Gozzini MD⁹ | Luigiana Luciano MD¹⁰ | Sara Galimberti MD, PhD¹¹ |
 Monica Bocchia MD, PhD¹² | Andrea Patriarca MD¹³ | Giuseppe Lanzarone MD¹⁴ |
 Bruno Martino MD¹⁵ | Anna Guella MD¹⁶ | Anna Rita Scortechini MD¹⁷ |
 Carmen Fava MD, PhD¹⁸ | Claudio Fozza MD, PhD¹⁹ | Simona Sica MD, PhD²⁰ |
 Nicola Di Renzo MD²¹  | Pellegrino Musto MD, PhD²² |
 Domenico Pastore MD, PhD²³ | Alessandro Maggi MD²⁴ | Michele Pizzuti MD²⁵ |
 Lorella Maria Antonia Melillo MD²⁶ | Angelo Michele Carella MD, PhD²⁷ |
 Giuseppe Tarantini MD²⁸ | Anna Mele MD²⁹ | Elisabetta Calistri MD³⁰ |
 Maria Rosaria Coppi MD³¹ | Fabio Saccona MSc² | Emilia Scalzulli MD³² |
 Beatrice Battaglio MD⁴ | Miriam Iezza MD³³ | Cinzia Bitetti MD³⁴ |
 Roberto Freilone MD¹ | Gianantonio Rosti MD³⁵ | Francesco Albano MD, PhD³⁶ |
 Fabrizio Pane MD, PhD³⁷ | Giorgia Specchia MD, PhD³⁶ |
 Giovannino Ciccone MD, PhD² | Giuseppe Saglio MD, PhD³⁸ | Massimo Breccia MD³² 

Correspondence

Valentina Gai, Division of Haematology,
 Azienda Ospedaliero Universitaria Città della
 Salute e della Scienza di Torino, Torino, Italy.
 Email: vgai@cittadellasalute.to.it

Funding information

Associazione Italiana Leucemia, Linfomi e
 Mieloma sezione di Bari

Abstract

Background: Improved outcome has been reported in chronic myeloid leukemia (CML) patients treated with tyrosine kinase inhibitors (TKIs) in sponsored trials.

Methods: This is a multicenter prospective cohort study of consecutive patients with newly diagnosed chronic phase CML from 19 regions in Italy. Baseline treatments and prognostic factors on time to first optimal molecular response ($\geq$ molecular response 3, MR3), time to disease progression, time to death from CML, and overall survival (OS) were analyzed using multivariable Fine and Gray models.

Results: The authors included 1433 CML patients: 49% (median age, 70 years) treated with frontline imatinib (IMA), and 51% treated with second-generation TKIs

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2025 The Author(s). *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society.

(2G-TKIs; median age, 52 years). EUTOS long-term survival (ELTS) was low in 68.1% of 2G-TKIs patients, compared to 50.4% of IMA patients. Faster molecular responses were observed with 2G-TKIs within the first 6 months and maintained thereafter (subhazard ratio [sHR], 1.31; 95% confidence interval [CI], 1.15–1.50). Female gender and low ELTS risk had faster time of response. Achieving major molecular response (MMR or MR3) was associated with reduced risk of progression at 6 and 12 months. Overall, 41 patients progressed without differences between IMA and 2G-TKIs. Intermediate and high risk ELTS showed higher risk of progression and death from CML. Twenty-two CML-related deaths (16.5%) occurred mostly in the first 2 years from diagnosis, higher in 2G-TKIs patients (sHR, 1.75; 95% CI, 0.52–5.87). OS at 5 years was 88% with no clear differences between IMA and 2G-TKIs treatment after adjustment for potential confounders.

Conclusions: The study confirms faster responses with 2G-TKIs compared to IMA but similar clinical outcomes and a strong prognostic effect of ELTS.

KEYWORDS

chronic myeloid leukemia, first-line treatment, imatinib, real-life study, risk factors, second generation TKI, TKI

INTRODUCTION

Over the past 2 decades, the prognosis of chronic myeloid leukemia (CML) patients in the chronic phase has significantly improved, with overall survival (OS) rates now approaching those of the general population.¹ This remarkable progress is attributable to the availability of an extensive therapeutic armamentarium² and a more profound understanding of the disease's molecular mechanisms.³ The European Leukemia Net (ELN) first introduced response milestones in 2006,⁴ and their most recent update in 2020⁵ has continued to guide the selection of first-line therapies and subsequent lines of treatment with tyrosine kinase inhibitors (TKIs), based on molecular response thresholds assessed at specific time points.

It is well established that patients achieving a *BCR::ABL1* transcript level of $\leq 10\%$ at 3 months exhibit near-normal OS.⁶ Additionally, patients reaching molecular milestones at later time points may still achieve excellent OS.¹ Conversely, those failing to meet milestones at 6 and 12 months typically receive an alternative TKI due to their worse prognosis.⁷ Indeed, recent studies have shown that patients failing to meet key molecular milestones ($> 10\%$ *BCR::ABL1*^{IS} at 6 months or $> 1\%$ *BCR::ABL1*^{IS} at 12 months) have significantly lower OS at 10–12 years compared to those achieving optimal responses.⁸

However, most of the available molecular and clinical data have been derived from clinical trials, which often do not fully capture the complexity observed in real-world populations.

The aim of the present study is to evaluate outcomes based on baseline risk factors and first-line treatment in a prospective, real-world cohort of CML patients enrolled in a collaborative Italian study (CML Italian Network).

MATERIALS AND METHODS

The CML Italian Network, comprising 68 Hematology Centers across 19 Italian regions, has prospectively collected clinical and biological data for all newly diagnosed adult (≥ 18 years) Philadelphia (Ph) + CML patients, diagnosed from January 2013 onward. The study was approved by local ethical committees. Data were recorded in a dedicated web-based database (<https://www.epiclin.it/lmc>). Baseline information included sociodemographic characteristics, clinical features, and standard laboratory results. All consecutive patients who provided written informed consent were included, with no exclusion criteria. Centers enrolling at least 10 patients and with updated follow-up were included in the current analysis. Sites are listed in Table S1.

For this study, patients were stratified into two groups based on initial treatment: those receiving imatinib (IMA) and those treated with second-generation TKIs (2G-TKIs: nilotinib, dasatinib, or bosutinib).

Molecular analyses were conducted and interpreted in accordance with international guidelines. Quantitative molecular responses of *BCR::ABL1*^{IS} were assessed using quantitative reverse transcription polymerase chain reaction performed in certified laboratories nationwide, with results expressed on the International Scale. For the purposes of this study, molecular responses achieving $\leq 0.1\%$ *BCR::ABL1*^{IS} (molecular response 3 (MR3) or better) were considered an end point for the current analyses.

Three time-to-event end points, specific to CML, were analyzed from the time of diagnosis: 1) time to first optimal molecular response ($\geq \text{MR3}$); 2) time to disease progression; and 3) time to

death from CML, with deaths classified as CML-related if disease progression was the reason. OS, defined as the time from diagnosis to death from any cause, was also assessed across the entire cohort. Patients alive at the last follow-up were censored at that time.

CML-specific outcomes were analyzed using competing risk methods as described by Gooley.⁹ In these analyses, we considered as competing events deaths from any cause for the analysis of time to first molecular response and deaths from non-CML-related causes for the analyses of time to disease progression and time to death from CML. Fine and Gray models were used to adjust comparisons for potential confounders. Additionally, Fine and Gray models were applied to evaluate the association between molecular responses at 6 and 12 months and the subsequent risk of CML progression, incorporating left truncation (landmark analysis) at the time point of the molecular assessment.

All multivariable models included a predefined set of variables capturing relevant prognostic factors at diagnosis, including age, sex, Charlson Comorbidity Index,¹⁰ ELTS risk score, and initial treatment (IMA vs. 2G-TKI).

Statistical analyses were performed using STATA software, version 15.0.

RESULTS

Characteristics of patients

From September 2013 to April 2024, 1433 newly diagnosed CML patients were prospectively enrolled (Table 1). Patients were followed for a median of 4.2 years.

At diagnosis, 702 patients (49%) were treated with IMA, and 731 patients (51%) received 2G-TKIs: nilotinib ($n = 414$; 28.9%), dasatinib ($n = 312$; 21.8%), or bosutinib ($n = 5$; 0.3%). The median age was 70 years (interquartile range [IQR], 58–77) in the IMA group and 52 years (IQR, 41–63) in the 2G-TKIs group. The proportion of male patients was comparable between the two groups (59% in the IMA group and 56% in the 2G-TKIs group).

The CCI revealed significant differences between groups. In the IMA group, 538 patients (76.6%) had a CCI score of 2–3, and 154 patients (21.9%) had a score of 4–5. In contrast, among the 2G-TKIs group, 662 patients (90.6%) had a CCI score of 2–3, and 54 (7.4%) had a score of 4–5. Data were missing for 25 patients (1.7%). Across the entire cohort, the most frequent comorbidities were cardiovascular disease ($n = 384$; 26.8%), pulmonary disease ($n = 164$; 11.4%), metabolic disease ($n = 126$; 8.8%), and other neoplasms ($n = 120$; 8.4%).

According to the EUTOS long-term survival (ELTS) score, risk distribution also differed between treatment groups. Among IMA-treated patients, 354 (50.4%) were low risk, 248 patients (35.3%) were intermediate risk, and 99 patients (14.1%) were high risk. Among those receiving 2G-TKIs, 498 patients (68.1%) were low risk, 156 patients (21.3%) were intermediate risk, and 76 patients (10.4%) were high risk. Data were missing for two patients.

TABLE 1 Baseline patient characteristics by first-line treatment in the cohort of CML patients.

	First-line treatment				Total (n = 1433)	
	Imatinib (n = 702)		2G TKIs (n = 731)			
	n	%	n	%	n	%
Age groups (years)						
<30	16	2.28	55	7.52	71	4.95
31–40	26	3.70	121	16.55	147	10.26
41–50	65	9.26	172	23.53	237	16.54
51–60	96	13.68	171	23.39	267	18.63
61–70	175	24.93	155	21.20	330	23.03
71–80	225	32.05	49	6.70	274	19.12
>80	99	14.10	8	1.09	107	7.47
Sex						
Male	414	58.97	411	56.22	825	57.57
Female	288	41.03	320	43.78	608	42.43
Comorbidities						
Cardiovascular disease	273	38.89	111	15.18	384	26.80
Pulmonary disease	128	18.23	36	4.92	164	11.44
Metabolic disease	93	13.25	33	4.51	126	8.8
Other neoplasm	75	10.68	45	6.16	120	8.4
CCI						
2	420	59.83	609	83.31	1029	71.81
3	118	16.81	53	7.25	171	11.93
4	99	14.10	34	4.65	133	9.28
≥5	55	7.83	20	2.74	75	5.23
Not available	10	1.42	15	2.05	25	1.74
ELTS						
Low risk	354	50.43	498	68.13	852	59.46
Intermediate risk	248	35.33	156	21.34	404	28.19
High risk	99	14.10	76	10.40	175	12.21
Not available	1	0.14	1	0.14	2	0.14

Abbreviations: CCI, Charlson Comorbidity Index; CML, chronic myeloid leukemia; ELTS, EUTOS long-term survival; TKI, tyrosine kinase inhibitor.

Molecular response

The time to achieve at least an MR3 response was compared between TKI classes. Figure 1A shows that patients treated with 2G-TKIs achieved MR3 or better responses faster than those receiving IMA. This advantage was evident within the first 6 months and remained constant thereafter, with an adjusted subhazard ratio (sHR) of 1.31 (95% CI, 1.15–1.50) (Table 2). Among other factors analyzed, male patients exhibited a slower time to response (sHR 0.80; 95% CI, 0.71–0.90), as

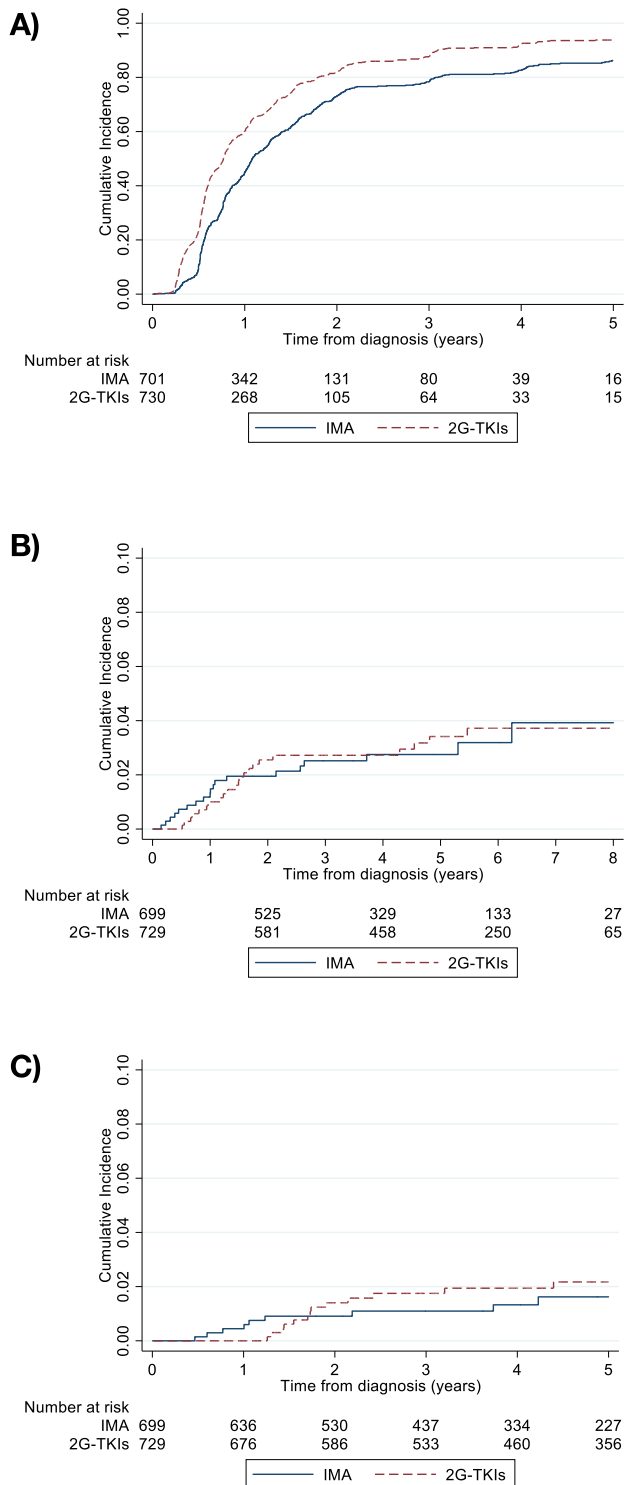


FIGURE 1 Cumulative incidence of time to molecular response ($\geq$ MR3) (A) since diagnosis of chronic myeloid leukemia (CML), estimated with the method by Gooley, considering deaths from any causes as competing events. Cumulative incidence of time to CML progression (B) and to CML-related deaths (C) since diagnosis of CML, estimated with the method by Gooley, considering the other causes of deaths as competing events.

did those with intermediate and higher ELTS scores (compared to low risk) and higher CCI. Achieving MR3 was associated with a trend of reduced risk of CML progression, both at 6 months (sHR 0.66; 95% CI, 0.26–1.70) and 12 months (sHR 0.47; 95% CI, 0.16–1.34).

Disease progression

Progression to accelerated phase (AP) or blastic phase (BP) occurred in 41 patients: 14 progressed to AP (3 deaths), and 27 progressed to BP (19 deaths). ELTS in progressed patients was low in 10 of 41 (24.4%), intermediate in 14 of 41 (34%) and high in 17 of 41 (41.5%). The cumulative incidence of progression was similar between treatment groups (Figure 1B), with a steeper slope during the first 18 months (reaching ~2%) and a slower increase thereafter (~2.5% at 4 years). No significant differences were observed between treatments (2G-TKIs vs. IMA: sHR 0.94; 95% CI, 0.40–2.21). The ELTS score remained the strongest predictor of progression risk (Table 2).

Notably, in the group of CML-related deaths (all in CP at baseline), five patients on 2G-TKIs were classified as intermediate and one patient was classified as low risk according to ELTS (Figure 2). Two of the five intermediate-risk patients underwent allogeneic bone marrow transplantation but relapsed and died; the other three patients were ineligible for transplantation and died of blastic disease as did the low-risk patient.

Nine of 22 patients who died from CML-related causes showed an ABL1 kinase domain mutation detected after disease progression, including four with T315I mutation. In addition, five of 22 patients had additional chromosomal abnormalities (ACA) at diagnosis and another seven patients had ACA at the time of progression.

Overall survival and CML-related deaths

The OS of the entire cohort is shown in Figure S1A. At 5 years, 88% (95% CI, 86–90) of patients were alive. As expected, patients treated with IMA had worse OS (Figure S1B), with a raw HR (2G-TKIs vs. IMA) of 0.27 (95% CI, 0.19–0.39, $p < .0001$) and an adjusted HR of 0.77 (95% CI, 0.52–1.16, $p = .216$) (Table S2), reflecting the confounding effect due to the older median age (+18 years compared to 2G-TKIs patients) and greater comorbidity burden of IMA-treated patients (Table 1). As expected, OS of high risk ELTS patients was worse compared to intermediate and low risk patients (Figure S1C). The causes of death differed significantly between groups (Table 3). Among 133 recorded deaths at 5 years, 22 (16.5%) were CML-related: nine of 98 (9.2%) in the IMA group and 13 of 35 (37.1%) in the 2G-TKIs group (Table 3; Figure 1C). Most CML-related deaths occurred due to disease progression within the first 2 years after diagnosis ($n = 17$; 77%). Progression beyond 2 years was rare, occurring in three IMA-treated and two 2G-TKIs-treated patients (Figure 2).

TABLE 2 Effects of baseline variables on time to response ($\geq$ MR3), time to progression, and time to death from CML.

Baseline variables	Time to response ($\geq$ MR3)			Time to progression			Time to death from CML		
	sHR ^a	95% CI	p	sHR ^b	95% CI	p	sHR ^b	95% CI	p
Age (per year)	1.00	1.00–1.01	.825	0.98	0.95–1.00	.081	1.00	0.97–1.04	.931
Sex, M (vs. F)	0.80	0.71–0.90	<.001	1.10	0.55–2.19	.785	1.35	0.51–3.59	.542
CCI (per unit)	0.87	0.81–0.93	<.001	1.17	0.94–1.46	.151	1.18	0.89–1.56	.258
ELTS intermediate (vs. low)	0.67	0.58–0.77	<.001	3.68	1.50–9.02	.004	5.47	1.34–22.40	.018
ELTS high (vs. low)	0.51	0.42–0.62	<.001	10.63	4.64–24.37	<.001	19.20	5.10–72.26	<.001
2G-TKIs (vs. IMA)	1.31	1.15–1.50	<.001	0.94	0.40–2.21	.895	1.75	0.52–5.87	.363

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; CML, chronic myeloid leukemia; ELTS, EUTOS long-term survival; F, female; M, male; sHR, subhazard ratio; TKI, tyrosine kinase inhibitor.

^asHRs adjusted for all the baseline variables in the table, estimated with a Fine and Gray model, considering deaths from any cause as competing events.

^bsHRs adjusted for all the baseline variables in the table, estimated with a Fine and Gray model, considering deaths from causes not CML-related as competing events.

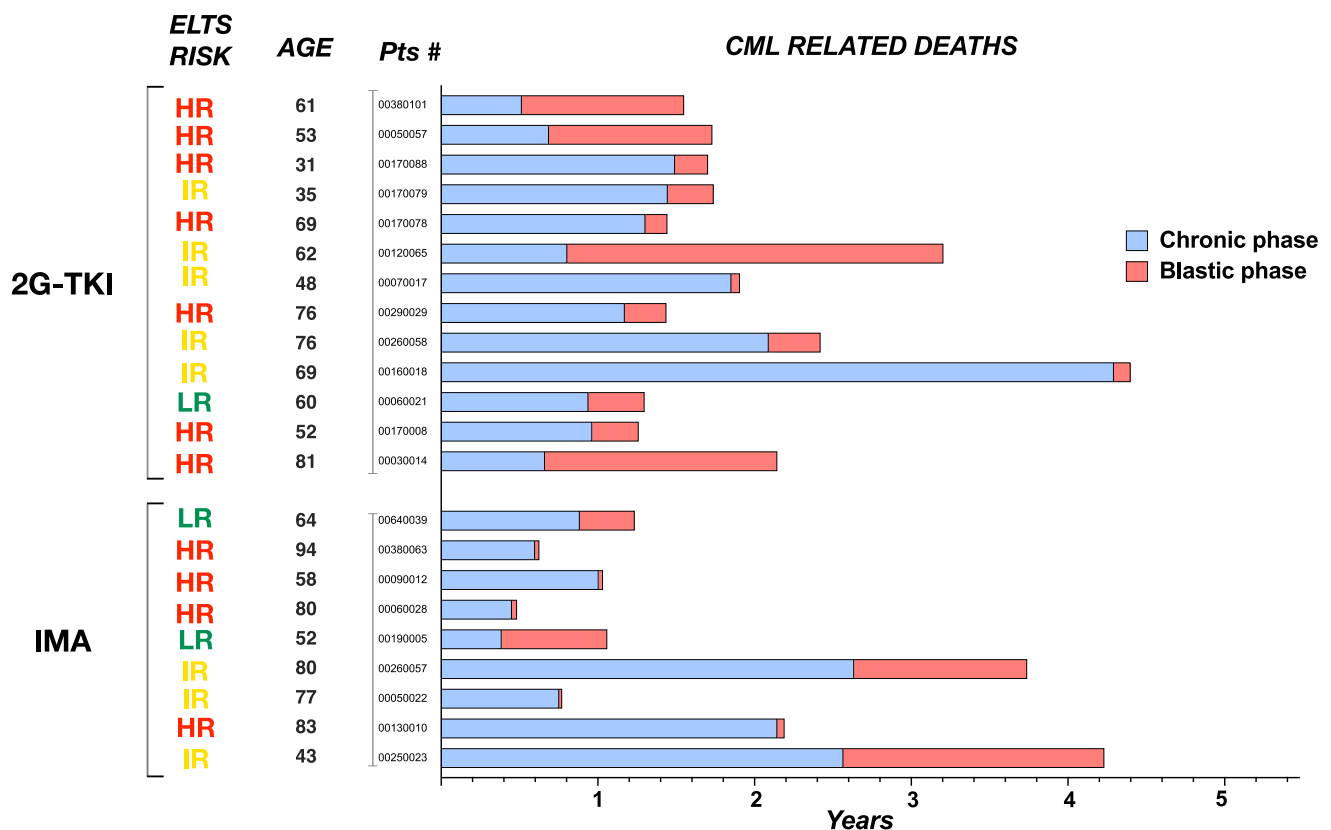


FIGURE 2 Description of the duration of the chronic and blastic phases in the 22 patients deceased from chronic myeloid leukemia, according to first-line treatment, EUTOS long-term survival (ELTS) risk, and age at diagnosis. Looking at ELTS risk, in the 2G-TKI group, seven were high risk (HR), five were intermediate risk (IR), and one was low risk (LR); in the IMA group, four were HR, three were IR, and two were LR.

The cumulative risk of CML-related deaths was slightly higher in the 2G-TKIs group (sHR 1.75); however, the small number of events introduced imprecision (95% CI, 0.52–5.87). Among the factors included in the multivariable model, the ELTS score emerged as the strongest predictor of CML-related mortality.

DISCUSSION

Currently, there are limited published data analyzing large, real-life CML cohorts, as most evidence originates from sponsored trials. In this study, we analyzed a prospective cohort of 1433 CML patients

TABLE 3 Causes of death of CML patients by first-line treatment.

Causes of death	First-line treatment				Total (n = 133)	
	Imatinib (n = 98)		2G TKIs (n = 35)			
	n	%	n	%	n	%
CML-related	9	9.2	13	37.1	22	16.5
Others	89	90.8	22	62.9	111	83.5
Cardiovascular	16	16.3	3	8.6	19	14.3
Metabolic	0	0.0	2	5.7	2	1.5
Pulmonary	7	7.1	0	0.0	7	5.3
Neoplasia	19	19.4	9	25.7	28	21.1
Bleeding	5	5.1	0	0.0	5	3.8
Nephrological	2	2.0	2	5.7	4	3.0
Infections	10	10.2	4	11.4	14	10.5
Gastrointestinal	1	1.0	0	0.0	1	0.8
Neurologic	4	4.1	0	0.0	4	3.0
Senectus	8	8.2	0	0.0	8	6.0
NA/other	17	17.3	2	5.7	19	14.3

Abbreviations: CML, chronic myeloid leukemia; NA, not available; TKI, tyrosine kinase inhibitor.

enrolled across 33 Italian hematological centers (Table S1). Consistent with previous reports, the median age at diagnosis in our cohort was 60 years.¹ Clinicians tended to select IMA for older patients, as reflected by the higher median age of 70 years in the IMA group compared to 52 years in patients treated with 2G-TKIs. This preference likely reflects IMA's well-established safety and tolerability profile,¹¹ making it a more suitable option for older patients with comorbidities, which were indeed more prevalent among IMA-treated patients in our study.

In terms of risk stratification, approximately 50% of IMA-treated patients were in the low-risk ELTS category, compared to 68% of patients in the 2G-TKI cohort. This discrepancy likely reflects the younger age in the latter group, as younger patients may have been preferentially treated with 2G-TKIs to facilitate deeper molecular responses and potential treatment discontinuation. These baseline differences in prognostic factors—especially age and comorbidities—strongly influence OS, necessitating a focus on specific CML-related outcomes.

As anticipated, patients treated with 2G-TKIs achieved MR3 or better responses more rapidly than those treated with IMA. This advantage was evident within the first few months of treatment and persisted throughout follow-up, with the difference remaining roughly constant. Male patients and those with higher comorbidity scores experienced slower responses. We tested the hypothesis that the lower average body weight of women might play a role, but the results of the multivariable models including weight at diagnosis did not support this explanation. In patients with older age and

comorbidity, we observed a trend toward more frequent intolerance and dose reduction of TKIs (data not shown) potentially responsible for slower responses.

Achieving MR3 by 6 or 12 months was associated with a trend to lower risk of CML progression. However, interpreting these findings in terms of causality is challenging.¹² Short-term surrogate end points, such as molecular responses, may simply reflect shared baseline predictors of later clinical outcomes.

Additionally, landmark analyses, commonly employed to mitigate immortal time bias, progressively select subsets of patients at different time points, potentially introducing bias.¹²

Progression to AP or BP was strongly correlated with baseline ELTS risk. Neither patient characteristics nor initial treatment choice (2G-TKI vs. IMA) significantly influenced progression risk (sHR 0.94, $p = .895$). This is clinically relevant, as approximately 50% of patients who experience progression ultimately die from CML. This finding aligns with previous highlighting the ELTS score as a robust prognostic tool^{13–15} but further exploration is needed to confirm these results in similar real-world populations.

The risk of CML-related death mirrored findings for disease progression, again underscoring the prognostic significance of the ELTS score (Figure 1C). Interestingly, the cumulative incidence of CML-related deaths plateaued after approximately 2 years, regardless of initial treatment. This suggests that the first 2 years of disease are critical for monitoring and managing CML-related events, especially in high-risk patients. Notably, half of all CML-related deaths (11 of 22, 50%) occurred in high-risk ELTS patients.

An interesting observation was the slightly higher risk of CML-related death in patients treated with 2G-TKIs (sHR 1.75, $p = .363$). This association, although imprecise due to the small number of events, may reflect a selection bias favoring 2G-TKIs in younger patients with more aggressive disease, a confounder that may not be fully controlled by the ELTS score. Additionally, it cannot be excluded that progression in 2G-TKI-treated patients may be less responsive to subsequent therapies, whereas IMA-treated patients might benefit more from second-line 2G-TKIs. This hypothesis is supported by the short time interval between progression and death observed in four of nine deceased 2G-TKI patients after progression, suggesting limited efficacy of subsequent treatments (Figure 2).

The 5-year OS for the entire cohort was 88%, consistent with prior studies.¹⁶ As expected, younger patients in the 2G-TKI group had superior OS (94%) compared to the IMA group (81%), but this difference was heavily confounded by age and comorbidity. When compared to registrative trials of 2G-TKIs, the OS in our cohort was similar for 2G-TKI-treated patient group but inferior for IMA-treated patients, likely due to differences in age and comorbidity distributions.^{17–19} These results are consistent with studies reporting similar OS in over 1500 IMA-treated patients.¹⁶

Of 133 total deaths, only 22 (16.5%) were CML-related deaths. The relative distribution of the other causes of death shows an excess in the IMA group for cardiovascular, pulmonary, and other age-related causes. Conversely, deaths from other neoplasms, metabolic, and neurological causes were relatively more frequent in

the 2G-TKI group. These findings underscore the importance of considering patient age, comorbidities, and causes of deaths when interpreting overall survival outcomes.

Our real-life study confirms the prognostic value of the ELTS score across all CML-related outcomes, also in a real-life context. The first 2 years of disease appear to be pivotal for prognosis and progressions occurring during this period. Beyond this time window, age and comorbidities predominantly influence survival through non-CML-related mortality.

Although 2G-TKIs and 3G-TKIs including asciminib²⁰ achieve faster molecular responses, this does not necessarily translate into lower progression rates or reduced CML-related mortality. The results of the ASC4FIRST trial showed an advantage of asciminib versus imatinib in the initial follow-up at 48 months, but how the drug will influence the future first line scenario remain a matter of discussion. The possibility that progression in 2G-TKI-treated patients may be less responsive to subsequent treatments warrants further investigation. Nevertheless, these findings could hold relevance especially for low- and middle-income countries.²¹ This study highlights the importance of individualized treatment strategies that balance molecular response objectives with clinical outcomes, considering patient-specific factors such as age, comorbidities, and baseline ELTS risk.

AUTHOR CONTRIBUTIONS

Valentina Gai: Conceptualization, investigation, writing—original draft, validation, methodology, and visualization. **Tiziana Rosso:** Conceptualization, software, methodology, data curation, formal analysis, and validation. **Fausto Castagnetti:** Investigation, writing—review and editing, and resources. **Patrizia Pregno:** Conceptualization, investigation, methodology, visualization, supervision, and writing—review and editing. **Massimiliano Bonifacio:** Investigation, writing—review and editing, and resources. **Isabella Capodanno:** Investigation, writing—review and editing, and resources. **Mario Tiribelli:** Investigation, writing—review and editing, and resources. **Fabio Stagno:** Investigation, writing—review and editing, and resources. **Giovanni Caocci:** Investigation, writing—review and editing, and resources. **Antonella Gozzini:** Investigation, writing—review and editing, and resources. **Luigiana Luciano:** Investigation, writing—review and editing, and resources. **Sara Galimberti:** Investigation, writing—review and editing, and resources. **Monica Bocchia:** Investigation, writing—review and editing, and resources. **Andrea Patriarca:** Investigation, writing—review and editing, and resources. **Giuseppe Lanzaone:** Investigation, writing—review and editing, and resources. **Bruno Martino:** Investigation, writing—review and editing, and resources. **Anna Guella:** Investigation, writing—review and editing, and resources. **Anna Rita Scortechini:** Investigation, writing—review and editing, and resources. **Carmen Fava:** Investigation, writing—review and editing, and resources. **Claudio Fozza:** Investigation, writing—review and editing, and resources. **Simona Sica:** Investigation, writing—review and editing, and resources. **Nicola Di Renzo:** Investigation, writing—review and editing, and

resources. **Pellegrino Musto:** Investigation, writing—review and editing, and resources. **Domenico Pastore:** Investigation, writing—review and editing, and resources. **Alessandro Maggi:** Investigation, writing—review and editing, and resources. **Michele Pizzuti:** Investigation, writing—review and editing, and resources. **Lorella Maria Antonia Melillo:** Investigation, writing—review and editing, and resources. **Angelo Michele Carella:** Investigation, writing—review and editing, and resources. **Giuseppe Tarantini:** Investigation, writing—review and editing, and resources. **Anna Mele:** Investigation, writing—review and editing, and resources. **Elisabetta Calistri:** Investigation, writing—review and editing, and resources. **Maria Rosaria Coppi:** Investigation, writing—review and editing, and resources. **Fabio Saccona:** Methodology, investigation, software, and data curation. **Emilia Scalzulli:** Investigation, writing—review and editing, and resources. **Beatrice Battaglio:** Investigation, writing—review and editing, and resources. **Miriam Iezza:** Investigation, writing—review and editing, and resources. **Cinzia Bitetti:** Investigation, writing—review and editing, and resources. **Roberto Freilone:** Investigation, writing—review and editing, and resources. **Gianantonio Rosti:** Investigation, writing—review and editing, and resources. **Francesco Albano:** Investigation, writing—review and editing, and resources. **Fabrizio Pane:** Investigation, writing—review and editing, and resources. **Giorgina Specchia:** Conceptualization, investigation, funding acquisition, methodology, validation, visualization, project administration, and supervision. **Giovannino Ciccone:** Conceptualization, methodology, software, formal analysis, data curation, writing—review and editing, validation, and visualization. **Giuseppe Saglio:** Conceptualization, validation, writing—review and editing, visualization, project administration, and supervision. **Massimo Breccia:** Conceptualization, investigation, writing—original draft, methodology, validation, visualization, writing—review and editing, and supervision. All the authors inserted data and discussed results, contributed to manuscript revision, and approved the submitted version.

AFFILIATIONS

¹Division of Haematology, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Torino, Italy

²Clinical Epidemiology Unit and CPO Piemonte, Città della Salute e della Scienza di Torino, Torino, Italy

³Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Institute of Hematology “L. & A. Seràgnoli”, Bologna, Italy

⁴Department of Medicine, Section of Hematology, University of Verona, Verona, Italy

⁵Hematology, AUSL Reggio Emilia, Reggio Emilia, Italy

⁶Division of Hematology and BMT, Azienda Ospedaliero-Universitaria di Udine, Udine, Italy

⁷Hematology Section AOU Policlinico “G. Martino”, University of Messina, Messina, Italy

⁸Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

⁹Hematology, University of Florence, Florence, Italy

¹⁰Hematology, Federico II University, Naples, Italy

- ¹¹Section of Hematology, Oncology, Transplant and Advances in Medicine, University of Pisa, Pisa, Italy
- ¹²Hematology and Transplants, University of Siena, Siena, Italy
- ¹³Department of Translational Medicine, Università degli Studi del Piemonte Orientale Amedeo Avogadro, Novara, Italy
- ¹⁴Division of Haematology, University of Torino, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Torino, Italy
- ¹⁵Hematology Unit, Azienda Ospedaliera "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy
- ¹⁶Hematology Department, Ospedale di Trento, Trento, Italy
- ¹⁷Department of Haematology, Ospedali Riuniti di Ancona, Ancona, Italy
- ¹⁸Università Degli Studi di Torino, Dipartimento di Scienze Cliniche e Biologiche, Scienze Cliniche e Biologiche, Torino, Italy
- ¹⁹Haematology, University of Sassari, Sassari, Italy
- ²⁰Ematologia e trapianto di cellule staminali emopoietiche, Università Cattolica del Sacro Cuore Facoltà di Medicina e Chirurgia, Rome, Italy
- ²¹Hematology, Vito Fazzi Hospital, Lecce, Italy
- ²²Department of Precision and Regenerative Medicine and Ionian Area, "Aldo Moro" University School of Medicine, Unit of Hematology and Stem Cell Transplantation, AOUC Policlinico, Bari, Italy
- ²³Division of Hematology, Hematology and Bone Marrow Transplant Unit, Brindisi, Italy
- ²⁴Hematology, Taranto Hospital, Taranto, Italy
- ²⁵Hematology division, Azienda Ospedaliera San Carlo, Potenza, Italy
- ²⁶Hematology, Ospedali Riuniti di Foggia, Foggia, Italy
- ²⁷Hematology and Stem Cell Transplantation Unit "Casa Sollievo della Sofferenza" Hospital, San Giovanni Rotondo (FG), Italy
- ²⁸Hematology, Hematology-Oncology, Barletta Hospital, Barletta, Italy
- ²⁹Hematology Unit, Azienda C. Panico, Tricase (Le), Italy
- ³⁰Division of Hematology, Dipartimento Medicina Clinica 1, Ospedale San Giacomo Apostolo, Treviso, Italy
- ³¹Hematology, Antonio Perrino Hospital, Brindisi, Italy
- ³²Hematology, Department of Translational and Precision Medicine, Az. Policlinico Umberto I-Sapienza University, Rome, Italy
- ³³Hematology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
- ³⁴Hematology, Presidio Ospedaliero "Madonna delle Grazie", Matera, Italy
- ³⁵IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) "Dino Amadori", Scientific Directorate, Meldola, Italy
- ³⁶Hematology, University of Bari, Bari, Italy
- ³⁷CEINGE Biotechnologie Avanzate and Department of Biochemistry and Medical Biotechnology, University of Napoli Federico II, Naples, Italy
- ³⁸Department of Clinical and Biological Sciences, University of Turin, Torino, Italy

ACKNOWLEDGMENTS

The study was supported by a grant from Associazione Italiana Leucemia, Linfomi e Mieloma (AIL) sezione di Bari. This study was approved by the local ethics committee at AOU Città della Salute e della Scienza, Torino, Italy. All patients provided written informed consent.

CONFLICT OF INTEREST STATEMENT

Valentina Giai served on advisory board for Novartis, Pfizer, and Incyte and received honoraria from Alexion, Sobi, and Roche.

Massimiliano Bonifacio received honoraria from Amgen and served on advisory board for Incyte, Novartis, Bristol-Myers Squibb, and Pfizer. Elisabetta Capodanno received honoraria from Incyte, Novartis, Bristol-Myers Squibb, and Celgene and served on advisory board for Pfizer. Fabio Stagno received honoraria for Speakers Bureau from Incyte and Novartis. Sara Galimberti received honoraria for supporting meetings from Novartis, AbbVie, Pfizer, Incyte, Astra Zeneca, Jazz, Celgene, Roche, and Janssen. Andrea Patriarca received honoraria from Sobi, Novartis, Roche, Incyte, Alexion, Takeda, Pfizer, Sanofi, and Bristol-Myers Squibb. Bruno Martino received honoraria for Speakers Bureau from Incyte, Astra Zeneca, Novartis, and Janssen. Claudio Fozza received research funding from Sanofi, Amgen, Bristol-Myers Squibb, and Sobi. Pellegrino Musto received consulting fees from Beigene. Gianantonio Rosti received honoraria for Speakers Bureau from Novartis, Incyte, and Pfizer. Fabrizio Pane received fees for consulting, membership on an entity's Board of Directors or advisory committees and Speakers Bureau from Incyte, Takeda, AbbVie, Amgen, Alexion, GSK, Bristol-Myers Squibb, Janssen, Jazz, Novartis, and Pfizer. Massimo Breccia received honoraria from Novartis, Incyte, Pfizer, AbbVie, Bristol-Myers Squibb, and AOP. Giuseppe Saglio received consulting fees and Speakers Bureau from Novartis, Hikma, and Ascentage Pharma. Monica Bocchia received consulting fees from Incyte Corporation and Novartis. Fausto Castagnetti received consulting fees from Bristol-Myers Squibb, Incyte Corporation, Novartis, and Pfizer. Maria Rosaria Coppi received fees for professional activities from the American Cancer Society. Anna Guella received fees for professional activities from APSS Trento. Giuseppe Lanzarone received travel fees from AbbVie, Jazz Pharmaceuticals, and Novartis. Fabio Saccona received fees for professional activities from AOU Città della Salute e della Scienza di Torino. Anna Rita Scortechini holds a copyright for "Chronic Myeloid Leukemia Outcomes According to Baseline Risk and First-Line Treatment in Real-World." Mario Tiribelli received consulting fees from Novartis; and received fees for professional activities from Bristol-Myers Squibb and Incyte Corporation. The others declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author on reasonable request.

ORCID

Valentina Giai  <https://orcid.org/0009-0009-4238-1300>

Massimiliano Bonifacio  <https://orcid.org/0000-0003-0716-1686>

Mario Tiribelli  <https://orcid.org/0000-0001-9449-2621>

Nicola Di Renzo  <https://orcid.org/0000-0003-0604-6934>

Massimo Breccia  <https://orcid.org/0000-0003-1163-6162>

REFERENCES

1. Cortes J, Pavlovsky C, Saußele S. Chronic myeloid leukaemia. *Lancet*. 2021;398:1914-1926.
2. Breccia M, Scalzulli E, Pepe S, Colafigli G, Martelli M. Future management of chronic myeloid leukemia: from dose optimization to new agents. *Curr Cancer Drug Targets*. 2022;22(10):796-805. doi:10.2174/156800962266220613144253

3. Cross NCP, Ernst T, Branford S, et al. European LeukemiaNet laboratory recommendations for the diagnosis and management of chronic myeloid leukemia. *Leukemia*. 2023;37(11):2150-2167. doi:[10.1038/s41375-023-02048-y](https://doi.org/10.1038/s41375-023-02048-y)
4. Baccarani M, Saglio G, Goldman J, et al. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood*. 2006;108(6):1809-1820. doi:[10.1182/blood-2006-02-005686](https://doi.org/10.1182/blood-2006-02-005686)
5. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia*. 2020;34(4):1-19. doi:[10.1038/s41375-020-0776-2](https://doi.org/10.1038/s41375-020-0776-2)
6. Marin D, Ibrahim AR, Lucas C, et al. Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. *J Clin Oncol*. 2011;30:232-238. doi:[10.1200/jco.2011.38.6565](https://doi.org/10.1200/jco.2011.38.6565)
7. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring. *Am J Hematol*. 2020;95(6):691-709. doi:[10.1002/ajh.25792](https://doi.org/10.1002/ajh.25792)
8. Lauseker M, Hehlmann R, Hochhaus A, Sauße S. Survival with chronic myeloid leukaemia after failing milestones. *Leukemia*. 2023;37(11):2231-2236. doi:[10.1038/s41375-023-02028-2](https://doi.org/10.1038/s41375-023-02028-2)
9. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med*. 1999;18(6):695-706. doi:[10.1002/\(sici\)1097-0258\(19990330\)18:6<695::aid-sim60>3.0.co;2-o](https://doi.org/10.1002/(sici)1097-0258(19990330)18:6<695::aid-sim60>3.0.co;2-o)
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383. doi:[10.1016/0021-9681\(87\)90171-8](https://doi.org/10.1016/0021-9681(87)90171-8)
11. Stempel JM, Shallis RM, Wong R, Podoltsev NA. Challenges in management of older patients with chronic myeloid leukemia. *Leuk Lymphoma*. 2024;65(9):1219-1232. doi:[10.1080/10428194.2024.2342559](https://doi.org/10.1080/10428194.2024.2342559)
12. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response and other comparisons of time-to-event by outcome variables. *J Clin Oncol*. 2008;26(24):3913-3915. doi:[10.1200/jco.2008.16.1000](https://doi.org/10.1200/jco.2008.16.1000)
13. Pfirrmann M, Clark RE, Prejzner W, et al. The EUTOS long-term survival (ELTS) score is superior to the Sokal score for predicting survival in chronic myeloid leukemia. *Leukemia*. 2020;34(8):2138-2149. doi:[10.1038/s41375-020-0931-9](https://doi.org/10.1038/s41375-020-0931-9)
14. Breccia M, Pregno P, Castagnetti F, et al. Eutos long-term survival score discriminates different Sokal score categories in chronic myeloid leukemia patients, showing better survival prediction. Analysis of the GIMEMA CML observational study. *Leukemia*. 2021;35(6):1814-1816. doi:[10.1038/s41375-021-01292-4](https://doi.org/10.1038/s41375-021-01292-4)
15. Zhang X-S, Gale RP, Huang X-J, Jiang Q. Is the Sokal or EUTOS long-term survival (ELTS) score a better predictor of responses and outcomes in persons with chronic myeloid leukemia receiving tyrosine-kinase inhibitors? *Leukemia*. 2022;36(2):482-491. doi:[10.1038/s41375-021-01387-y](https://doi.org/10.1038/s41375-021-01387-y)
16. Hehlmann R, Lauseker M, Sauße S, et al. Assessment of imatinib as first-line treatment of chronic myeloid leukemia: 10-year survival results of the randomized CML study IV and impact of non-CML determinants. *Leukemia*. 2017;31(11):2398-2406. doi:[10.1038/leu.2017.253](https://doi.org/10.1038/leu.2017.253)
17. Kantarjian HM, Hughes TP, Larson RA, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. *Leukemia*. 2021;35(2):1-14. doi:[10.1038/s41375-020-01111-2](https://doi.org/10.1038/s41375-020-01111-2)
18. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-year study results of DASISION: the dasatinib versus imatinib study in treatment-naïve chronic myeloid leukemia patients trial. *J Clin Oncol*. 2016;34(20):2333-2340. doi:[10.1200/jco.2015.64.8899](https://doi.org/10.1200/jco.2015.64.8899)
19. Brummendorf TH, Cortes JE, Milojkovic D, et al. Bosutinib versus imatinib for newly diagnosed chronic phase chronic myeloid leukemia: final results from the BFORE trial. *Leukemia*. 2022;36(7):1825-1833. doi:[10.1038/s41375-022-01589-y](https://doi.org/10.1038/s41375-022-01589-y)
20. Hochhaus A, Wang J, Kim D-W, et al. Asciminib in newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2024;391(10):885-898. doi:[10.1056/nejmoa2400858](https://doi.org/10.1056/nejmoa2400858)
21. Malhotra H, Radich J, Garcia-Gonzalez P. Meeting the needs of CML patients in resource-poor countries. *Hematology*. 2019;2019(1):433-442. doi:[10.1182/hematology.2019000050](https://doi.org/10.1182/hematology.2019000050)

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gai V, Rosso T, Castagnetti F, et al. Chronic myeloid leukemia outcomes according to baseline risk and first-line treatment in real-world settings: data from the Italian Network/CML Campus. *Cancer*. 2025;e35963. doi:[10.1002/cncr.35963](https://doi.org/10.1002/cncr.35963)